

Amendments to the Specification:

Replace the paragraph beginning at page 3, line 28, with the following amended paragraph:

The present invention results more particularly from the demonstration by the applicant of a novel human protein, referred to as PAP1 (Parkin Associated Protein 1), or LY111, which interacts with parkin. The PAP1 protein (sequence SEQ ID NO: 1 or 2) shows a certain homology with synaptotagmins and is capable of interacting more particularly with the central region of parkin (represented on the sequence SEQ ID NO: 3 or 4). The PAP1 protein has also been cloned, sequenced and characterized from various tissues of human origin, specifically lung (~~SEQ ID NO: 12, 13~~) and brain (~~SEQ ID NO.: 42, 43~~12, 13) tissue, as well as short forms, which correspond to splicing variants (SEQ ID NO: 14, 15, 44,~~45~~).

Replace the paragraph beginning at page 5, line 11, with the following amended paragraph:

For the purposes of the present invention, the name PAP1 protein refers to the protein per se, as well as to all homologous forms thereof. "Homologous form" is intended to refer to any protein which is equivalent to the protein under consideration, of varied cellular origin and in particular derived from cells of human origin, or from other organisms, and which possesses an activity of the same type. Such homologs also comprise natural variants of the PAP1 protein of sequence SEQ ID NO 2, in particular polymorphic or splicing variants. Such homologs can be obtained by experiments of hybridization between the coding nucleic acids (in particular the nucleic acid of sequence SEQ ID NO: 1). For the purposes of the invention, a sequence of this type only has to have a significant percentage of identity to lead to a physiological behavior which is comparable to that of the PAP1 protein as claimed. "Significant percentage of identity" is intended to refer to a percentage of at least 60%, preferably 80%, more preferably 90% and even more preferably 95%. As such, variants and/or homologs of the sequence SEQ ID NO: 2 are described in the sequences SEQ ID NO: 13~~[[,]]~~ and 15, ~~43 and 45~~, and are identified from tissues of human origin. The name PAP1 therefore also encompasses these polypeptides.

Replace the paragraph beginning at page 7, line 7, with the following amended paragraph:

In a particular embodiment, they are compounds which are capable of interfering with the interaction between the region of parkin which is represented on the sequence SEQ ID NO: 4 and the region of the PAP1 protein which is represented on the sequence SEQ ID NO: 2, 13~~[[,]]~~ and 15, ~~43 or 45~~.

Replace the paragraph beginning at page 7, line 27, with the following amended paragraph:

According to a first preferred embodiment, the compounds of the invention are peptide compounds comprising all or part of the peptide sequence SEQ ID NO: 2 or a derivative thereof, in particular all or part of the peptide sequence SEQ ID NO: 13~~[[.]]~~ and 15, ~~43 or 45~~ or derivatives of these sequences, more particularly of the PAP1 protein, which comprises the sequence SEQ ID NO: 2, 13~~[[.]]~~ and 15, ~~43 or 45~~.

Replace the paragraph beginning at page 8, line 3, with the following amended paragraph:

For the purposes of the present invention, the term "derivative" refers to any sequence which differs from the sequence under consideration because of a degeneracy of the genetic code, which is obtained by one or more modifications of genetic and/or chemical nature, as well as any peptide which is encoded by a sequence which hybridizes with the nucleic acid sequence SEQ ID NO: 1, or a fragment of this sequence, for example with the nucleic acid sequence SEQ ID NO: 12~~[[.]]~~ or 14~~[[.]]~~ ~~42 or 44~~ or a fragment of these sequences, and which is capable of interfering with the interaction between the PAP1 protein, or a homolog thereof, and parkin. "Modification of genetic and/or chemical nature" can mean any mutation, substitution, deletion, addition and/or modification of one or more residues. The term "derivative" also comprises the sequences which are homologous to the sequence under consideration, which are derived from other cellular sources and in particular cells of human origin, or from other organisms, and which possess an activity of the same type. Such homologous sequences can be obtained by hybridization experiments. The hybridizations can be carried out with nucleic acid libraries, using the native sequence or a fragment of this sequence as probe, under varied conditions of hybridization (Maniatis *et al.*, 1989). Moreover, the term "fragment" or "part" refers to any portion of the molecule under consideration, which comprises at least 5 consecutive

residues, preferably at least 9 consecutive residues, even more preferably at least 15 consecutive residues. Typical fragments can comprise at least 25 consecutive residues.

Replace the paragraph beginning at page 10, line 4, with the following amended paragraph:

A specific subject of the present invention relates to the PAP1 protein. It is more particularly the PAP1 protein comprising the sequence SEQ ID NO: 2 or a fragment or derivative of this sequence, for example the PAP1 protein, sequence SEQ ID NO: 13~~[[,]]~~ or 15~~[[,]]~~ 43, 45 or fragments of these sequences.

Replace the paragraph beginning at page 10, line 26, with the following amended paragraph:

The antibodies according to the invention are more preferably capable of binding the PAP1 proteins which comprise the sequence SEQ ID NO: 2~~[[,]]~~ or 13, 43 ~~or~~ 45 in particular.

Replace the paragraph beginning at page 11, line 12, with the following amended paragraph:

A subject of the present invention is also any nucleic acid which encodes a peptide compound according to the invention. It can be, in particular, a nucleic acid comprising all or part of the sequence which is presented in SEQ ID NO: 1, 12, or 14, 42 ~~or~~ 44 or a derivative thereof. For the purposes of the present invention, "derived sequence" is intended to mean any sequence which hybridizes with the sequence which is presented in SEQ ID NO: 1, or with a fragment of this sequence, and which encodes a peptide compound according to the invention, as well as the sequences which result from the latter by degeneracy of the genetic code. For example, nucleic acids according to the invention comprise all or part of the nucleic sequence SEQ ID NO: 12~~[[,]]~~ or 14, 42 ~~or~~ 44.

Replace the paragraph beginning at page 13, line 21, with the following amended paragraph:

For the purposes of the invention, a particular nucleic acid encodes a polypeptide comprising the sequence SEQ ID NO: 2 or a fragment or derivative of this sequence, in particular the human PAP1 protein. It is advantageously a nucleic acid comprising the sequence SEQ ID NO: 1~~[[,]]~~ or 12, 14, ~~42 or 44~~.

Replace the paragraph beginning at page 16, line 20, with the following amended paragraph:

The claimed sequences can be used in the context of gene therapies, for transferring and expressing, *in vivo*, antisense sequences or peptides which are capable of modulating the interaction of the PAP1 protein with parkin. In this respect, the sequences can be incorporated in viral or nonviral vectors, which allows their administration *in vivo* (Kahn *et al.*, 1991). As viral vectors in accordance with the invention, mention may be made most particularly of adenovirus, retrovirus, adeno-associated virus (AAV) or herpes virus type vectors. A subject of the present application is also recombination-defective viruses comprising a nucleic acid which encodes a polypeptide according to the invention, in particular a polypeptide or peptide comprising all or part of the sequence SEQ ID NO: 2 or of a derivative of this sequence, for example all or part of the sequence SEQ ID NO: 12~~[[,]]~~ or 14, ~~42 or 44~~ or derivatives of these sequences.

Replace the paragraph beginning at page 34, line 5, with the following amended paragraph:

In order to confirm the presence of a full-length Ly111b transcript in the human brain, a PCR was performed from complementary DNA taken from human fetal brain (Marathon Ready cDNA, Clontech), using the oligonucleotides LyF1 (AAT GGA AGG GCG TGA CGC, Figure 5, SEQ ID NO: 38) and HA71 (CCT CAC GCC TGC AAC CTG, SEQ ID NO: 39) as primers. A DNA fragment with low representation of approximately two kilobases was amplified. The product of this first PCR served as a matrix for a nested

PCR, carried out with oligonucleotides LyEcoF (GCACGAATTC ATG GCC CAA GAA ATA GAT CTG, SEQ ID NO: 41) and HA72 (CTG TCT TCG TAT TTC TCC GCC TTG, SEQ ID NO: 41). The amplified products were digested with the restriction enzymes EcoRI (integrated into the oligonucleotide LyEcoF) and BstEII (Figure 5) and inserted into the expression vector pcDNA3, then their sequence was determined. Analysis of the clone sequences obtained revealed the presence of two potential full-length Ly111b transcripts in the human fetal brain (Figure 5). The first of these transcripts (Ly111b_{fullA}) corresponds to the mRNA which was identified in the human lung (Example 6) and encodes a 609 amino acid protein (pLy111b_{fullA}; Figures 5, 6, ~~SEQ ID NO: 42-43~~). The second (LY111b_{fullB}) probably represents an alternative splicing product of a common primary mRNA. In this transcript, which is identical to LY111b_{fullA}, the sequence between the nucleotides 752 and 956 of the sequence validated in the human lung is absent (~~SEQ ID NO: 42~~). LY111b_{fullB} thus encodes a 541 amino acid protein (pLY111b_{fullB}) (SEQ ID NO: 50) which is identical to pLY111_{fullA} (SEQ ID NO: 48), in which, however, the domain included between amino acids 172 and 240 (Figures 5, 7, ~~SEQ ID NO: 44-45~~) is missing. The two proteins pLY111b_{fullA/fullB} integrate into the domain of interaction with the fragment of parkin which comprises amino acids 135 to 290, which were identified in the yeast (initial sequence LY111b Figure 5), and can therefore theoretically maintain this interaction.